

REMARKS

Applicants submit this Amendment / Reply with the accompanying Request for Continued Examination (RCE) filed herewith for consideration and entry of the foregoing amendments. Applicants also wish to thank the Examiner for the courtesy extended to Applicants' attorney, Jeffrey Hsi, during the March 21, 2002 telephone interview.

Claims 1-28 are pending in this application. Applicants have amended claims 1, 3, 4, 5, 8, 12, 13, 14, 16, 20, 21, 22, 24 and 28, and added claims 29-31, in order to expedite prosecution of this application to more clearly delineate the claimed subject matter. These amendments are made without waiver or prejudice to future prosecution in later applications claiming priority from this application. Support for these amendments appears throughout the specification and claims as originally filed. No new matter is introduced by these amendments.

Rejection under 35 U.S.C. 102(b)

Claims 1 - 4, 13, and 21 are rejected as being anticipated by Yamaguchi et al. U.S. Patent No. 3,765,906 ("Yamaguchi"). It is alleged in the Action that: Yamaguchi teaches a culture medium containing rice powder in which a *Monascus* species is inoculated.

The allegation is based on an oversimplification of the assertion above. Yamaguchi teaches a submerged culture medium containing 2% rice powder (e.g., Example 1 in Yamaguchi) used for cultivating a *Monascus* species, however, inherent in such teaching is the fact that the Yamaguchi medium is a homogeneous liquid medium, not a solid substrate medium. Further, Yamaguchi clearly teaches rice (see, column 3, line 40; column, 5, line 44) in powder form for use in their processes.

Applicants' subject matter relates to use of the grain (e.g., rice) as "full-grain rice particles". See, throughout the specification, including at page 7, lines 22-23 (direct comparison of rice particles versus rice powder); page 8, line 24; page 9, line 18; page 10, lines 16-17; and page 11, line 28. Thus, Applicants' solid substrate medium comprising a "full- grain particle" as delineated in independent claims 1, 13, and 21, and discussed throughout the specification as filed in terms of "suspended nutritionally solid substrate" or "grains", including at page 5, line 26

to page 6, line 11, and at page 8, lines 17-19, respectively, is distinguishable from Yamaguchi's powdered form. Applicants' nutritionally solid substrate is a substrate (i.e., "full-grain particle") which keeps its solid morphology in the medium to provide a place where mycelia can attach to. See, Specification at page 5, lines 26-28. A liquid medium containing rice powder does not contain a substrate which keeps its solid morphology.

Moreover, not only are the physical differences between the liquid (Yamaguchi's) and solid (Applicants') mediums evident, but the functional differences in the two mediums are also demonstrated in Example 1 at page 7 of Applicants' specification as filed. The results recited in Applicants' Example 1 show that red pigments produced by using the medium containing suspended full-grain rice particles (i.e. Applicants' solid medium) were two-fold greater than those produced by using a rice powder-containing medium (i.e., liquid medium, Yamaguchi). See, Specification at page 8, lines 15-17.

Based on the foregoing remarks, Applicants submit that Applicant's claimed subject matter is distinguishable from (both physically and functionally), and not anticipated by, Yamaguchi. Applicants request withdrawal of this rejection.

Rejection under 35 U.S.C. 103(a)

Claims 6, 11-12, 19-20, and 27-28 are rejected as being unpatentable over Yamaguchi et al. U.S. Patent No. 3,765,906 ("Yamaguchi") in view of Johal et al. U.S. Patent No. 4,954,440 ("Johal") and Eyal et al. U.S. Patent No. 5,077,201 ("Eyal"). In the Action, it is alleged that Yamaguchi teaches a nutritionally solid substrate that is provided in a culture medium in which a *Monascus* species is inoculated, then it is alleged that Johal provides motivation for adding other materials (e.g., nitrogen source, nutrients, etc.) as well as the use of batch fermentation and the fed batch process, and finally it is alleged that Eyal further supports the motivation to employ the fed batch process. Applicants disagree.

As delineated above in response to the rejection under 35 U.S.C. 102(b), the allegation of the teaching of Yamaguchi is an oversimplification and inaccurate, which inaccuracy forms the underlying basis of this rejection. The teaching of Yamaguchi relates to a homogeneous liquid medium, not a solid substrate medium. Applicants' nutritionally solid substrate (i.e., "full-grain particle solid substrate") is a substrate that keeps its solid morphology in the medium to provide

a place where mycelia can attach. A homogeneous liquid medium containing rice powder does not contain a substrate that keeps its solid morphology. Yamaguchi provides no motivation in regard to "full-grain particle solid substrates" and certainly provides no indication of the greatly improved yield (i.e., two-fold increase in pigment production) that results from the use of full-grain solid substrates. It is Applicants who first disclose the advantage of utilizing full-grain solid substrates (see, Specification Example 1) to provide this advantageous and surprising activity. Moreover, neither Johal nor Eyal discuss use of a "full-grain particle solid substrate" and certainly provide no indication of the greatly improved yield (i.e., two-fold increase in pigment production) that results from the use of full-grain particle solid substrates. In fact, Johal relates to supports that are "fixed" and "chemically and/or biologically inert" (see, Johal at column 3, lines 58-61), clearly teaching away from Applicants' full-grain particle solid substrates, which are not inert. **As such, Applicants submit that Yamaguchi, in view of Johal and Eyal, does not render Applicants' subject matter obvious, and request that this rejection be withdrawn.**

Claims 5, 7-8, 14-16, and 22-24 are rejected as being unpatentable over Yamaguchi in view of Yueh et al. U.S. Patent No. 4,418,080 ("Yueh") and Haas et al. U.S. Patent No. 4,031,250 ("Haas"). In the Action, it is alleged that Yamaguchi teaches a nutritionally solid substrate that is provided in a culture medium in which a *Monascus* species is inoculated, then it is alleged that Yueh provides motivation for obtaining an inoculum from a stock culture, and finally it is alleged that Haas provides motivation for a stock culture grown on an agar slant. Applicants disagree.

As delineated above in response to the rejection under 35 U.S.C. 102(b), the allegation of the teaching of Yamaguchi is an oversimplification and inaccurate, which inaccuracy forms the underlying basis of this rejection. The teaching of Yamaguchi relates to a homogeneous liquid medium based on rice powder, not a solid substrate medium (i.e., Applicants' use of "full-grain particles"). Applicants' full-grain particle solid substrate is a substrate that keeps its solid morphology in the medium to provide a place where mycelia can attach. A homogeneous liquid medium containing rice powder does not contain a substrate that keeps its solid morphology. Yamaguchi provides no motivation in regard to "full-grain particle solid substrates" and certainly provides no indication of the greatly improved yield that results from the use of full-

grain particle solid substrates. It is Applicants who first disclose the advantage of utilizing full-grain particle solid substrates (see, Specification Example 1) to provide this advantageous and surprising activity.

Yueh, or Haas, also does not suggest Applicants' subject matter, that is, "full-grain particle solid substrates." Yueh discusses use of "steel cut and tempered wheat, wheat flour, pearled barley or barley flour." See, Yueh at column 1, lines 53-55. Haas does not discuss any advantage relating to grain size. Thus, neither Yueh nor Haas discuss nor intimate the type of surprising improvement disclosed by Applicants' use of "full-grain particle solid substrates." **As such, Applicants submit that Yamaguchi, in view of Yueh and Haas, does not render Applicants' subject matter obvious, and request that this rejection be withdrawn.**

Claims 9-10, 17-18, and 25-26 are rejected as being unpatentable over Yamaguchi in view of Yueh, Haas, and further in view of Tung et al. Bioprocess. Eng. 17(1) pp.1-5 (1997) ("Tung"). In the Action, the same allegations regarding Yamaguchi in view of Yueh and Haas (above) are reiterated, and then it is further alleged that while the above references do not teach the use of a pneumatic airlift bioreactor with a net draft tube, use of such a bioreactor would have been obvious in light of Tung. Applicants disagree.

For the reasons stated above, Applicants submit that Yamaguchi in view of Yueh and Haas do not render claims 9-10, 17-18, and 25-26 obvious. For that reason alone, the rejection further based in view of Tung should be withdrawn. Nonetheless, Tung also provides no teaching that use of their bioreactor is useful for *Monascus* species (Tung teaches *Saccharomyces cerevisiae*) nor is any indication made as to what specific processes are particularly amenable for use in their bioreactor. In fact, it is stated in Tung that "[e]xtension of the proposed reactor to other aerobic fermentation processes is possible" (underline added for emphasis) and that "[t]he performance of the airlift reactor with multiple (more than two) concentric net draft tubes requires further investigations." See, Tung at page 4 (last paragraph). Not only does Tung lack a teaching of Applicants' methods as appropriate conditions suitable for their bioreactor, it appears that Tung generally is unclear as to what processes are viable in their bioreactor. Moreover, Tung provides no teaching of Applicants' "full-grain particle solid substrate" methods and the surprising greatly improved yields (i.e., two-fold increase in pigment production) produced thereby. **As such, Applicants submit that Yamaguchi, in view of Yueh,**

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Page : 9

Attorney's Docket No.: 08415-003001 / 0470-5039-US

Haas, and Tung does not render Applicants' subject matter obvious, and request that this rejection be withdrawn.

Attached is a marked-up version of the changes being made by the current amendment.

Applicants ask that all claims be examined. Should the claims not be found to be in condition for allowance, the Examiner is encouraged to contact Applicants' undersigned attorney, collect, to discuss the application. Applicants thank the Examiner in advance for such courtesy extended.

Enclosed is a \$27 check for excess claim fees and a \$200 check for the Petition for Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing attorney docket number 08415-003001.

Respectfully submitted,

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Version with markings to show changes made

In the claims:

Claims 1, 3, 4, 5, 8, 12, 13, 14, 16, 20, 21, 22, 24 and 28 have been amended as follows:

-- 1. (Amended) A method for cultivation of filamentous fungi comprising the steps of:

(a) preparing a medium comprising a [suspended nutritionally] full-grain particle solid substrate; and

(b) inoculating said medium with said filamentous fungi in a bioreactor to carry out fermentation wherein the mycelia of said filamentous fungi are attached to said [suspended] full-grain particle solid substrate.

3. (Amended) The method as claimed in claim 1, wherein said [nutritionally] full-grain particle solid substrate is a carbohydrate.

4. (Amended) The method as claimed in claim [3]1, wherein said carbohydrate is [grain]rice.

5. (Amended) The method as claimed in claim 4, further comprising the steps of husking, cocking, and sterilizing said [grain]rice before adding to said medium.

8. (Amended) The method as claimed in claim 7, wherein the culturing comprises:

(1) inoculating said filamentous fungi from a stock culture to a new agar plate and incubating in an incubator for about 5 to 7 days;

(2) washing spores and mycelia of the filamentous fungi grown on said plate with sterile water; and

(3) cultivating for about 36 to 48 hours said spores and mycelia in a medium comprising a [nutritionally] full-grain particle solid substrate by shaking, to form a culture.

12. (Amended) The method as claimed in claim 11, wherein the medium of the batch comprises a nitrogen source and a [nutritionally] full-grain particle solid substrate.

13. (Amended) A method for cultivation of *Monascus* species by using a [suspended] full-grain particle solid grain substrate comprising the steps of:

(a) preparing a medium comprising a [suspended] full-grain particle solid grain substrate; and

(b) inoculating said medium with said *Monascus* species in a bioreactor to carry out fermentation wherein the mycelia of said *Monascus* species are attached to said [suspended] full-grain particle solid grain substrate.

14. (Amended) The method as claimed in claim 13, further comprising the steps of husking, cocking, and sterilizing said full-grain particle solid grain before adding to said medium.

16. (Amended) The method as claimed in claim 15, wherein the culturing comprises:

(1) inoculating said *Monascus* species from a stock culture to a new agar plate and incubating in an incubator for about 5 to 7 days;

(2) washing spores and mycelia of said *Monascus* species grown on said plate with sterile water; and

(3) cultivating for about 36 to 48 hours said spores and mycelia in a medium comprising a full-grain particle solid grain substrate by shaking, to form a culture.

20. (Amended) The method as claimed in claim 19, wherein the medium of the batch comprises a nitrogen source and a full-grain particle solid grain substrate.

21. (Amended) A method for producing metabolites from the cultivation of *Monascus* species by using a [suspended] full-grain particle solid grain substrate comprising the steps of:

(a) preparing a medium comprising a [suspended] full-grain particle solid grain substrate; and

(b) inoculating said medium with said *Monascus* species in a bioreactor to carry out fermentation wherein the mycelia of said *Monascus* species are attached to said [suspended] full-grain particle solid substrate.

22. (Amended) The method as claimed in claim 21, further comprising the steps of husking, cocking, and sterilizing said full-grain particle solid grain before adding to said medium.

24. (Amended) The method as claimed in claim 23, wherein the culturing comprises:

(1) inoculating said *Monascus* species from a stock culture to a new agar plate and incubating in an incubator for about 5 to 7 days;

(2) washing spores and mycelia of said *Monascus* species grown on said plate with sterile water; and

(3) cultivating for about 36 to 48 hours said spores and mycelia in a medium comprising a full-grain particle solid grain substrate by shaking, to form a culture.

28. (Amended) The method as claimed in claim 27, wherein the medium of the batch comprises a nitrogen source and a full-grain particle solid grain substrate.--